A CLINICO PATHOLOGICAL STUDY OF MALIGNANT MELANOMA

Dissertation
Submitted in partial fulfillment of the regulations of

M.S. DEGREE EXAMINATION

BRANCH I GENERAL SURGERY

Department of General Surgery

GOVT. STANLEY MEDICAL COLLEGE AND HOSPITAL

CHENNAI - 600001

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

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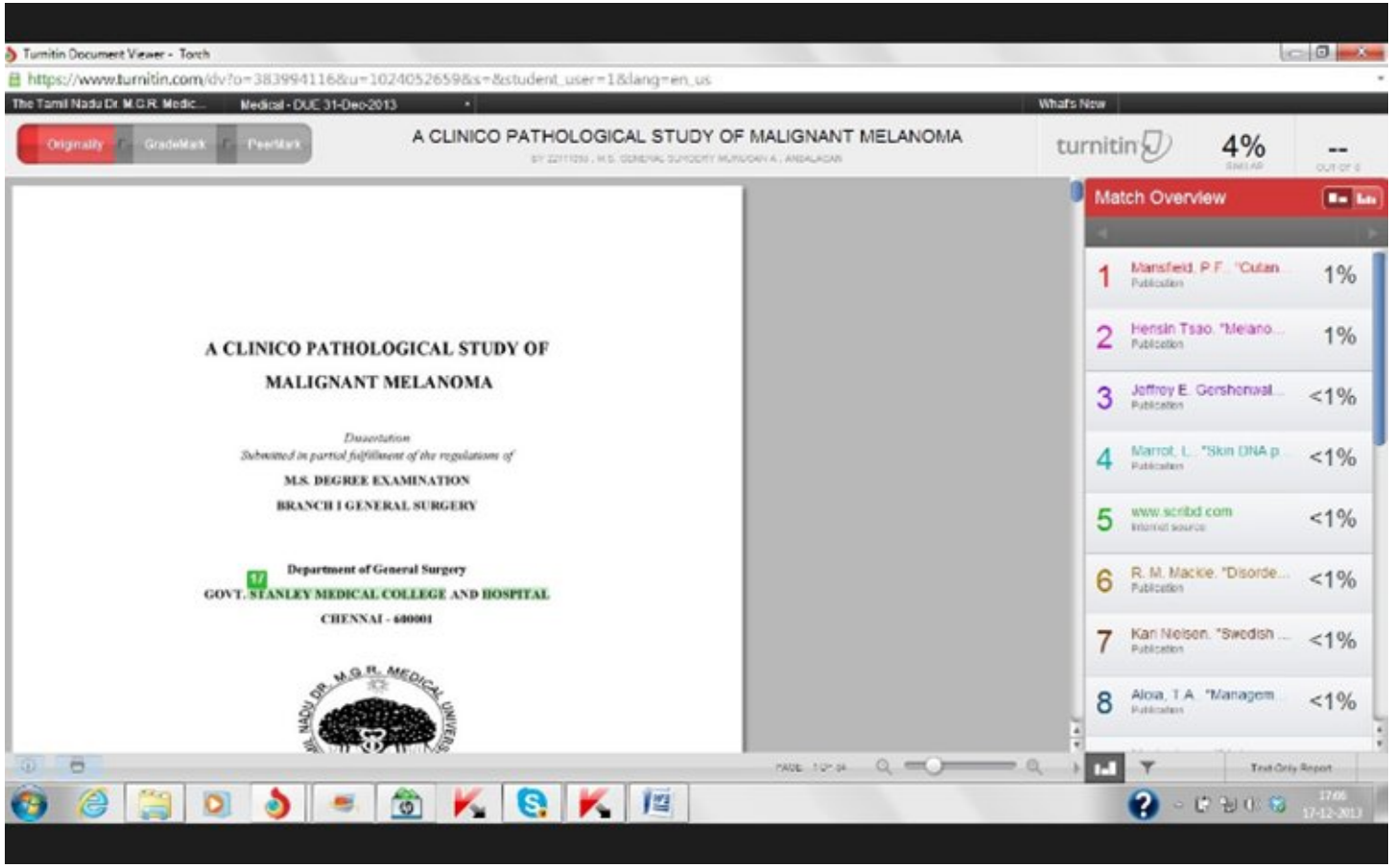
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is the bonafide work done by Dr. A.Murugan ., Post Graduate student (2011 – 2014) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfillment of the regulations of The Tamil Nadu Dr. M.G.R Medical University, Chennai for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

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DECLARATION

I, DR. A. MURUGAN solemnly declare that this dissertation titled

A CLINICO PATHOLOGICAL STUDY OF MALIGNANT MELANOMA is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief.

Prof. S.VISWANATHAN, M.S.,
Professor of Surgery

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

Place: Chennai.
Date: December 2013. DR. A. MURUGAN

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A CLINICO PATHOLOGICAL STUDY OF MALIGNANT MELANOMA

INTRODUCTION

A malignant melanoma (MM) is a melanocyte-derived cancer, which most often is found in the skin (cutaneous malignant melanoma, CMM) but can be found in all organs that harbour melanocytes, e.g. the ears, the eyes, the mucosal membranes (nose, oral cavity, anorectal mucosa and the genitourinary mucosa), the central nervous system (leptomeningeal melanoma) and in the gastrointestinal tract. It is the most malignant skin cancer type and causes the majority of skin cancer related deaths. CMM is among the most common types of cancer in young adults.

AIM OF STUDY

- TO KNOW THE INCIDENSE OF MALIGNANT MELANOMA IN OUR HOSPITAL
- TO STUDY THE VARIOUS MODES OF PRESENTATION OF MALIGNANT MELANOMA
- TO ASSESS THE PROGNOSTIC FACTORS IN ORDER OF IMPORTANCE OF SURVIVAL SUCH AS LYMPH NODE STATUS, ULCERATION AND THICKNESS.
- TO EVALUATE THE VARIOUS TREATMENT MODALITIES AND THEIR COMPLICATIONS, PROGNOSIS OF MALIGNANT MELANOMA IN OUR HOSPITAL

MATERIALS AND METHODS

Cases admitted in all surgical units of department of general surgery, dermatology department, plastic surgery department and oncology department in Stanley government hospital between may 2011 to December 2013 were taken in a random fashion for this study. This group of 30 patients were aged between 30 to72 years with a mean age of 50 yrs. Of these 18 were male and 12 female.

RESULTS

These 30 patients were divided into two main group. Group A were curative resection was planned and Group B were palliative treatment was planned.

GROUP A

Included 24 patients for curative resection

- no distant visceral metastasis

- no local fixity to surrounding important structures

- no fixed regional lymphnode

GROUP B

Included 6 patients for palliative treatment

- Palliative resection (2 patients)
- Palliative chemotherapy (2 patients)
- Palliative radiotherapy (3 patients)

CONCLUSION

- Mean age at presentation was 50 years
- 46.6% of patients had stage 3 disease at presentation
- Most of the cases in this series are extremities melanoma
- Curative wide local excision was possible in 63.3% of cases
- Blackish patches, ulcer and growth were the commonest complaints
- Prognosis of the patients in my study better in patients without ulceration and lymph node involvement

KEYWORDS

Malignant melanoma, wide local excision, radical lymph node dissection, satellite nodule, in transit lesion, skin, oral cavity, anal canal.

INTRODUCTION

A malignant melanoma (MM) is a melanocyte-derived cancer, which most often is found in the skin (cutaneous malignant melanoma, CMM) but can be found in all organs that harbour melanocytes, e.g. the ears, the eyes, the mucosal membranes (nose, oral cavity, anorectal mucosa and the genitourinary mucosa), the central nervous system (leptomeningeal melanoma) and in the gastrointestinal tract. It is the most malignant skin cancer type and causes the majority of skin cancer related deaths. CMM is among the most common types of cancer in young adults.

Melanomas can arise de novo in the skin (about 70%) or have a common nevus or a clinically atypical nevus as a precursor lesion. As long as the CMM grows in the epidermis the tumour is characterized as in situ, but when it grows down in the dermis it is invasive with a potential to metastasize. The histopathological examination of a melanoma always includes the measure of depth in millimetre, according to Breslow, and the measure of invasion to different skin layers (I to V), according to Clark .

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- TO REVIEW THE LITERATURE ON MALIGNANT MELANOMA

REVIEW OF LITERATURE

ANATOMY

The human skin is the largest organ with a surface area of 1.4-2m and consists of the three layers epidermis, dermis and subcutaneous tissue.In the skin hair follicles, sweat and sebaceous glands are found and the three basal layers are complemented and joined by three networks that link the skin to the rest of the body: cutaneous nerves, cutaneous blood vessels and lymphatics. These three networks provide e.g. nutrition and oxygen supply, and are vital for fluid balance, immune responses and skin sensation. The skin constitutes an important barrier against outer dangers as mechanical trauma, infections, chemical irritants, microorganism, Ultraviolet radiation (UVR) and free radicals (which can cause toxicity to DNA and cell membranes), toxins and heat.

The most superficial part of the skin is the epidermis, an avascular layer, mainly composed of keratinocytes (KC) as well as smaller populations of pigment producing melanocytes (MC) and mechano sensory Merkel cells. The immune system is also present in the epidermis, as the migratory Langerhans cells and intra epidermal T-cells. Beneath the epidermis is the dermo epidermal junction with the

basal layer, and underlying this is the dermis, which mainly consists of connective tissue with eccrine glands and hair follicles, dermal fibroblasts and a nerve, complex network of vessels. The third layer of the skin is the subcutaneous fat , providing a hormone factory and thermal insulation and acting as a shock absorber.

Melanocytes

Melanocytes are the neural crest-derived dendritic cells, which are present in the epidermis, in the uveal tract, in the leptomeninges , in the hair follicles and in the inner ear. They can also be found in the mucosal membranes and in gastrointestinal tract and common for all anatomical sites is that increased numbers of melanocytes. In the epidermis they are not unevenly dispersed along the basal layer at the dermo epidermal junction, where approximately every 8th cell is a melanocyte. This pigment production determines human hair and skin colour and protects the receiving cells nuclei/DNA from damage by UV light. The way that melanin protects the DNA is by absorption and scattering of the UVR . One melanocyte takes care of and provides melanin to up to 36 KCs in the surrounding area, named the epidermal melanin unit . They produce the pigment melanin (for melanogenesis see below) within melanosomes, organelles that are transferred to

surrounding keratinocytes and hair follicle cells. The synthesis and transfer of melanin are regulated by several paracrine and autocrine factors, in response to both endogenous and exogenous stimuli, where UVR is one important factor . The melanocytes are also susceptible to UVR and oxidative stress, factors that may cause genetic mutations in the melanocytes and thus capable of inducing malignant transformations.

Melanin synthesis

Melanin is produced in three versions , DHI-melanin [black] and the reddish-yellow pheomelanin and the brown-black eumelanins (DHICA-melanin [brown]. They have different functions where eumelanin is photoprotective and acts as a scavenger to Reactive Oxygen Species (ROS), unlike pheomelanin that is probably harmful after UVR exposure, via the generation of ROS and free radicals. The amino acid tyrosine is catalyzed by tyrosinase to DOPA/DOPA quinone and further to eumelanin or pheomelanin, depends upon the, level of cyclic AMP (cAMP) ,the presence of cysteine and activity of tyrosinase. Tyrosinase catalyzes the conversion of L-tyrosine to DOPA and further to DOPAquinone, which is required for the synthesis of both eumelanin and pheomelanin. The formation of pheomelanin

requires the presence of cysteine as well as less tyrosinase activity and less cyclic AMP (cAMP) than does the formation of eumelanin. DHICA-eumelanin is brown, DHI-eumelanin is black.The key factor in the production of melanin is the amino acid tyrosine, rate-limiting enzyme for melanogenesis are tyrosinase. The activity of tyrosinase is increased by DOPA and is stabilized by tyrosinase related protein 1. If the tyrosinase gene (TYR) is mutated, no melanin can be produced leads to type 1b oculo cutaneous albinism . Several factors, including e.g. α-MSH (α-melanocyte stimulating hormone, see below), Agouti signalling protein (ASP/ASIP), endothelin-1 (ET-1), basic fibroblast growth factor (bFGF) and UVR, influence the activity of the most important proteins involved in the melanogenesis (Park et al. 2009). The type and ratio of melanin produced (eu/pheo) depends on several different 16 melanogenic enzymes, the melanosome proteins (e.g. P protein and TRP1) and the availability of cysteine.

Basal Skin Pigmentation (skin colours)

The human skin colours/photo types are mainly dependent on the content and type of melanin distributed to the KCs, and on factors produced by KCs to regulate pigmentation .

EPIDEMIOLOGY

In Australia, which has the highest CMM incidence rates worldwide, the age-adjusted incidence rates were 34.6 (women) and 46.1 (men) per 100 000 individuals in year 2005 (AIHW/AACR 2008). In Sweden cutaneous melanoma was the sixth and eighth most common cancer in women and men respectively in 2007, and the latest reported incidence of invasive melanoma was 2333 cases (1182 women, 1151 men). The intra epidermal melanomas (in situ) added another 1146 cases (606 women, 540 men) (Social styrelsen 2008). The last reported average annual increase of all cancers in Sweden was 1.1% for women and 1.7% for men, but for melanoma this increase was 3.8% for women and 3.6% for men and thereby the most rapidly increasing malignant tumour in Sweden . This rapid increase is evident also in other fair-skinned populations all over the world . The corresponding numbers in Sweden 2007 approached 24 (women) and 26.5 (men) per 100 000individuals, reflecting that Sweden has some of the highest rates after Australia and New Zealand .

RISK FACTORS

Multiple risk factors play a major role for development of malignant melanoma.

1. Skin type
2. Age
3. Gender
4. Tanning bed use
5. Previous melanoma
6. Sunlight exposure
7. Benign nevi
8. Family history
9. Genetic predisposition
10. Atypical mole and melanoma syndrome

SKIN TYPE

Skin, eye and hair phenotypes

Red/blond hair, freckles, and blue/grey eye coloured people had more risk. Present fair skin, poor tanning ability, often additionally light/red hair, light eye colours.

These phenotypic characteristics are well known to have an association with the genes that regulate skin colour and pigmentation. One of these key genes is MC1R (see above). while others are only associated with red hair or red hair/fair skin but not with melanoma (Raimondi et al. 2008) risk factors that have been studied are e.g. indicators of actinic skin damage and a history of a previous premalignant or invasive nonmelanoma skin cancer (NMSC) (i.e. Actinic keratoses [AK], Squamous Cell Carcinoma [SCC]). These risk factors are also indicators of cumulative sun exposure. In addition, the freckling phenotype is also closely connected to the amount of UVR that the individuals have been exposed to (Gandini et al. 2005). This stresses the delicate balance between hereditary and environmentally causes of melanoma.

Immunosuppression individuals with an immune deficiency (e.g. organ transplant recipients with immunosuppressive therapy and individuals with HIV/AIDS) have an increased risk to develop cancer, and the risk of melanoma has been shown to be 1.24 in HIV/AIDS patients and 2.34 in transplant patients. The comparable risk of NMSC was 4.11 for HIV/AIDS patients and 28.62 for transplant patients . Inherited susceptibility to melanoma/Genetics About 90 % of all melanomas are sporadic and only 10% of all cases of melanoma occur in patients who have a hereditary predisposition for melanoma In the high-risk melanoma-prone families several cases of melanoma are present in multiple generations. The affected family members often develop multiple primary melanomas and are diagnosed at a younger age than non-familial sporadic cases. The observed increased melanoma risk in relatives of melanoma cases is probably caused by both genetic factors and shared environmental exposure 1995).

Skin phototypes

The skin phototypes are classified according to UVR reaction. Dark skin contains the same number and density of MCs as fair skin, and the basal pigmentation (“constitutive pigmentation”) thus depends on the level of the melanogenic activity of the MCs and on the transfer

of elanosomes to the surrounding KCs. This activity is mirrored in the number of produced melanosomes and in the efficiency of transporting the melanosomes to the KCs. The size of the melanosomes (smaller in fair skin), the type of melanin produced (eumelanin/pheomelanin ratio) and the rate of melanosome-degradation (occurring in mid-epidermis) of the KCs (smaller degrades faster) are also important element in the basal pigmentation. Eumelanin is present in large amounts in individuals with dark skin and hair. Whereas pheomelanin predominates in people with lower skin types 1 and 2.

UVR exposure results in alpha Melanocyte stimulating hormone , cortico tropic hormone and Endothelin release from the keratinocytes (KCs). α-MSH andACTH bind to the Melanocortin-1-receptor (MC1R), increase cyclic AMP (cAMP) and activate Protein kinase A (PKA), finally leading to increased levels of tyrosinase and hence increased eumelanin synthesis. UVR also damages the DNA of the cells, thereby activating the tumour protein p53 (TP53)-pathway to enhance DNA repair, apoptosis and allow for cell arrest. ETR=Endothelin receptor, MEK/ERK Mitogen-activated protein kinase2/Extracellular signal-regulated kinase.

Melanoma incidence ten times more common in caucasians than African Americans. seven times more common in caucasians than the melanoma incidence of American Hispanics. In addition, while patients with light skin, red or blond hair, or blue eyes are more prone for increased risk of melanoma.

AGE

The incidence of melanoma is 1.6 fold lower for men than women before 40years of age. At more than 65 years men is more incidence of melanoma than women.

GENDER

In general, men is higher incidence than female. 1.5 times higher risk for development of melanoma in male than a female risk.

TANNING BED USE

At more than 30 years or older, tanning bed use more than ten times of risk. Younger patients who use annually more than ten times of tanning and more than six times the risk of developing melanoma compared with who do not use tanning beds. Number of years, hours and sessions directly proportional to increased risk of developing

melanoma. Since 2010, the WHO lists use of tanning beds as a carcinogen.

Facultative Skin Pigmentation (Tanning)

Tanning is when pigmentation increases above baseline as an effect of UVR exposure .Tanning ability is highly influenced by the genes responsible for skin pigmentation and thus the response to UVR, where mutated genes e.g. lead to defect melanin production or defect response to receptor stimulation. UVR affects MCs both direct and indirect (via effect on KCs). These events finally elevate the responsiveness of the MCs to α-MSH, increase eumelanin synthesis and enhance melanosome transfer and UVR exposure to existing pheomelanin leads to the production of ROS/free radicals , which probably contributes to the increased incidence of CMM and NMSC observed in red hair colour (RHC) phenotypes . More specifically, Ultraviolet A radiation (UVA, 320-400 nm) is thought to mediate one of its tanning effects through oxidation of pre-existing melanin, which results in immediate pigment darkening (which fades after 8 hours). Delayed tanning is visible 48 to 72 hours after UVA and Ultraviolet B radiation (UVB,290-320 nm)) exposure, which is dependent on new

melanin formation via increased transcription of essential factors and eventually increased tyrosinase activity.

Alpha Melanocyte stimulating hormone

Alpha-MSH is one of the melanocortin peptides (α-MSH, ACTH, and beta-endorphin),which plays an important role in the melanogenesis by inducing MC differentiation and melanin production.

All melanocortin peptides are produced by the proteolytic cleavage of the precursor protein POMC (Pro Opio MelanoCortin) and exert their effects through melanocortin receptors (MCR, see below). α-MSHis produced in the pituitary gland, but also in the human skin by KCs, MCs and Langerhans cells. Increased production of α-MSH by KCs is seen after UVR exposure .α-MSH together with ET-1 have been shown to: activate the KT-pathway (a prosurvival signalling pathway), enhance DNA repair (nucleotide excision repair [NER]), inhibit production of ROS and DNA photo products after UVR exposure and finally to promote eumelanin synthesis. Insummary, all these functions lead to increased survival of MCs after UV irradiation.

Melanocortin-1 receptor/MC1R

There are five major human melanocortin receptors and the most common seen on the surface of melanocytes is the melanocortin-1 receptor (MC1R). The wild type allele of the MC1R that is predominant in the African continent is associated with dark skin and hair, as a result of promoted eumelanin production. When α-MSH (or ACTH) binds to a functional MC1R, the levels of cAMP increase and the levels of tyrosinase and several melanogenic enzymes are increased by transcription. With plenty of tyrosinase around, the synthesis of eumelanin is favoured instead of pheomelanin.The phenotypic advantages, with MC1R-variants, lighter skin and bright/red hair colours in northern countries with scarce UV radiation, are thought to be related to the vitamin D synthesis and the bone meta bolism .

PREVIOUS MELANOMA

Risk of developing second melanoma is 3 to 7% in patient have previous melanoma. This risk is compared in general population is more than 800 times in patients with previous melanoma.

SUNLIGHT EXPOSURE

Increased risk of malignant melanoma associated with sun exposure, but a clear relationship has not been associated with malignat melanoma unlike basal cell carcinoma and squamouos cell carcinoma who exposed to cumulative sun exposure. Number of severe and painful sunburn exposure is directly related with the increased risk of malignant melanoma. Patients who have a history of greater than eight severe sunburn are more risk of developing melanoma. Sunlight effect is directly related to uv-B radiation but uv-A radiation role, has not been completely excluded.

History of sunburns (due to skin type)

Intermittent sun exposure and history of severe sunburn were most strongly associated with melanoma while occupational (cumulative) exposure seemed to be protective in some studies (Gandini et al. 2005). One biologic explanation to the effect of intermittent exposure is that it causes DNA damage in MCs but not enough to cause apoptosis. An accumulation of genetic mutations caused by incomplete DNA repair from every intermittent exposure could lead to malignant transformation over time. The risk associated with use of sunbeds is debated, as most epidemiological studies have found an

increased risk, especially in young users, but some have not . One hypothesis is that host response to UVR is more important than the dose and type of UVR exposure. In addition, it is problematic to estimate the individual's exposure to UVR in retrospective studies, as study participants estimate the used amounts of sunscreen, the amount of UVR exposure and when the UVR exposure occurred subjectively and sometimes after a long latency. Moreover, multiple sunburns during childhood and adolescence and the increased risk of melanoma associated with that, might be influenced of recall bias and modified by the phenotype.

BENIGN NEVI

Who presented with more than 50 nevi, all of which are more than 2 mm in diameter have 15 times the melanoma risk of persons with less than 5 nevi. Benign nevi not a precursor of melanoma.

FAMILY HISTORY

A family history of melanoma increases five times risk of developing melanoma .

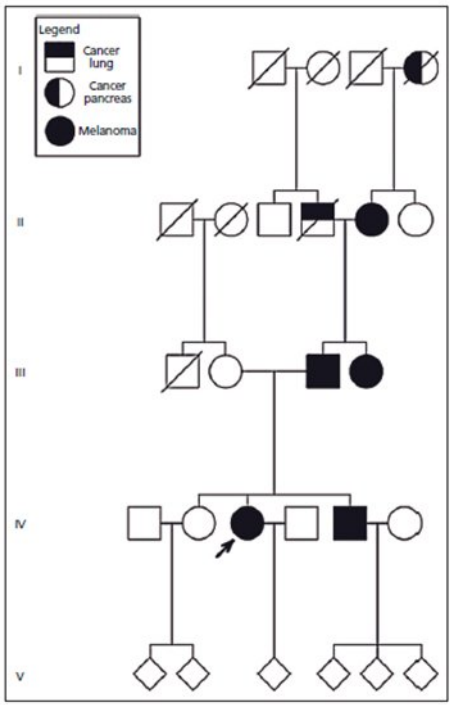
The ratio of sporadic and familiar melanoma.

The high-risk melanoma-prone families are under intense research and several underlying genes have been revealed. The melanoma genetics consortium, GenoMEL (www.genomel.org) is an organisation with melanoma research groups from 14 countries around the world pooling data, in order to elucidate the genetic field of melanoma and with a special interest for familiar melanoma.

GENETIC PREDISPOSITION

The heritable genes for melanoma susceptibility can vary from rare high-risk, high-penetrance genes to low-risk, low-penetrance genes

It is thought that the high-risk, high penetrance genes are responsible for the rare familial melanomas but not for the sporadic cases, which are instead probably caused by more common allelic variants ("polymorphisms") in the moderate risk or low-risk. Some of the genes will be highlighted below.



A family tree from a family with a heritdatary mutation in the CDKN2A gene, which is a high risk gene for melanoma.

Black circles-female melanoma , Male circles-male melanoma

CDKN2A-p16 MC1R CCND1 (cyclin D1) - High-risk genes

CDKN2A- p14ARF PTEN- High-risk genes

CDK4 MITF- Moderate risk gene

Rb / RB BRAF- Moderate risk gene

NRAS - Low-risk genes

TP53 - Low-risk genes

CDKN2A-the major high-risk gene. The major gene involved in melanoma development is the tumour suppressor gene CDKN2A, mentioned above (see cell signalling networks, Figures 7, 8.). Studies have shown that this high-risk gene is mutated in 20-40% of melanoma prone families (with ≥3 members affected by melanoma), as compared to a mutation frequency of about 1-2 % in population-based melanoma patients. Mutations in the gene have also been linked to an increased risk of other tumours as e.g. pancreatic cancer (PC) and breast cancer . The encoded two gene products (p16, which is a negative regulator of cell cycle progression, and p14ARF which stabilizes p53) are both tumour suppressors.

The second gene product p14ARF binds to and prevents human double minute-2 (HDM2) from accelerating the degradation of p53, thus possessing tumour suppressive effects. p53 normally senses genetic damage and allows pause for DNA repair or activates apoptosis if there is too much DNA damage. Decreased p53 leads to genetic instability when mutations and other genetic damage are left. A mutated p14ARF does not inhibit HMD2, which in turn accelerates the destruction of p53 and thus enhances growth and survival of altered/damaged cells instead of cell cycle arrest and apoptosis. Families with mutations in the exon

1β resulting in a mutated p14ARF protein have e.g. shown an association between melanoma and neural system tumours

CDK4 and RB/Rb--other high-risk genes

As mentioned, the normal p16 protein binds to (and inhibits) the action of CDK4.Mutations in the CDK4 gene make the CDK4 resistant to p16 inhibition and thus give the same phenotypic results as for a non-functional p16. Not inhibited CDK4 interacts with CCND1 and phosphorylates the RB/Rb protein, hence making RB/Rb inactive and allowing cells to unregulated pass the G1/S check point . Moreover, CDK4 amplification has been observed in sporadic melanomas, especially in acral and mucosal melanomas (Curtin et al. 2005). Families with germline mutations in the retinoblastoma gene (RB1), especially inherit a risk for retinoblastomas, but individuals who survive the retinoblastoma tumour also have a high risk for developing melanomas, as RB/Rb no longer can bind E2F and prevent unregulated cell division. ARB1mutation is found in approximately 6 % of sporadic melanomas .

ATYPICAL MOLE AND MELANOMA SYNDROME

Clinically Atypical nevi (CAN)

Clinically atypical nevi/Atypical moles/Clark nevi/Dysplastic nevi are all names for the same nevus entity, but there is still no consensus on the nomenclature of this group. A problem is that the clinical features all too often do not correspond to the histopathological features, as a clinically atypical nevus can lack histological 22signs of dysplasia and vice versa. The histo pathological criteria are thus controversial without any general agreement .Clinically, CAN are pigmented macules, papules or plaques, most common on the scalp and trunk and with clinical features resembling melanoma such as asymmetry, red-brown-black colour, faded, indistinct or notched borders, fried egg appearance with a papule within a macula, concentric circles resembling a target(cockade nevus) and diameter > 5mm. An estimated two to eight percent of the population have CAN in the US, while one study from northern Sweden Showed a population-based prevalence of 11% . Another study from the Swedish west coast reported population-based figures of as high as 18%. The onset of CAN is usually in older children and young adults and can be sporadic (non familial), as well as familial or part of a syndrome. The presence of atypical nevi independently indicates a higher risk of melanoma, as

they can be both markers of and possibly even potential precursors for melanoma .

In case-control studies (which have shown an excess prevalence of CAN in melanoma cases relative to controls) and in cohort studies (which have shown an excess in melanoma incidence both in familial melanoma kindreds with CAN and in patients with sporadic CAN relative to the general population) this correlation, with a higher melanoma risk, has been observed . More over, there seem to be a dose-response relation between melanoma risk and the total number of CAN. The causal genes that create the phenotype with excess CAN have not yet been fully elucidated, but several candidates exist. Data suggests possible linkage to loci on chromosomes 5, 7 and 9.

Atypical mole syndrome (AMS)

The observation that individuals with melanoma, from melanoma-prone families, often had an abnormal nevus phenotype with multiple common and atypical nevi/moles was first described in 1978 by Clark as the “B-K-mole syndrome”. This phenotype has later been variously known as the dysplastic nevus syndrome (DNS) or the atypical mole syndrome (AMS). Different definitions of the same syndrome have been proposed, and thus literature is sometimes difficult to compare, but in 1983 Kraemer et al described a further subdivision of

the DNS, dependent on different melanoma risk categories, and on how many individuals per kindred that were affected by melanoma and atypical nevi, respectively . The initial study about the BK-mole syndrome referred e.g. to the last category “D-2”, but often different categories are intended when studies in general are referring to AMS/DNS, and the non-specific nomenclature can be confusing as AMS/DNS can be demonstrated both as a sporadic form and in different familial settings, and simultaneously with or without melanoma(s) . Description of the sporadic and the subgroups of the familial Atypical Mole Syndromes/ Dysplastic Nevus Syndromes, according to Kraemer et . The subgroup “D-2” is the group that is most commonly referred to as the “AMS/DNS”, when this is mentioned in familial studies. DN= dysplastic nevus, DNS= Dysplastic nevus syndrome, AN=Atypical Nevus, MM= malignant melanoma Just as the description of the syndrome is some what arbitrary, different authors have differently described the characteristics of the AMS phenotype . However, most authors define the phenotype as one that presents “large numbers“ of common nevi over 2 mm in diameter and ≥2 CAN. Nevertheless, a more specific scoring system has been developed by Bishop et al. In conclusion, the presence of the AMS phenotype is associated with an increased risk of melanoma, both in the general population (as sporadic AMS/DNS) and in families.

CLINICAL PRESENTATION

Clinical features of melanoma include color changes , irregular raised surface, increase size of lesion and surface ulceration. Physical examination particularly emphasis on the scalp, web space, intertriginous areas. A biopsy should be done on any pigmented lesion that undergos a change in size and color change. Nodal region, satellite and in transit lesion present in advanced melanoma

PATHOGENESIS

Pathogenesis of the MC transformation into a melanoma cell is complex and the exact mechanisms are still not wholly understood. Both inherited and somatic 33 genetic events probably contribute, as well as environmental factors and increased production of ROS in the MC.

At least three changes are required to transform a MC into an invasive melanoma;

(i) something that initiates clonal expansion of the MC (e.g. mutations in proto oncogenes)

(ii) events that make the MC overcome cell senescence (e.g. influencing cell-cycle control)

(iii) something that reduces or suppresses the apoptotic ability of the MCs (Bennett 2008).

If mutagenic DNA in the MC escapes repair before cell division and if the cell cycle regulating mechanisms simultaneously cease to function, the melanocytes with DNA damage begin to divide in an uncontrolled manner, thus leading to the formation of a melanocytic

tumour, a melanoma. Hence, dys regulations of the MC cell cycle control, of cell signalling mechanisms and aberrations in transcriptional control are all mechanisms underlying the oncogenesis of melanoma, together with other factors as availability of nutrients, activation of cell surface receptors and level of cellular stress. Recent research has also added theories about melanoma stem cells, which might probably change the view upon melanoma pathogenesis in the future. The mechanisms involved (so far known) will be briefly reviewed below.

Three cell signalling networks; CDKN2A/RAS/Apoptosis

Three major, interacting, signalling networks have been shown to be important:

(i) The tumor constraining CDKN2A network,

(ii) The growth-promoting RAS signalling network and

(iii) The key downstream regulator of apoptosis, the BCL-2 and p53 network . The tumour-limiting CDKN2A network;

One of the major genes involved in melanoma pathogenesis is found on chromosome 9 (9p21), and the gene is called CDKN2A (formerly MTS1/p16/p16[INK4A]). The gene (OMIM#600160) encodes two gene products through alternative splicing: p16/INK4A

and p14ARF (alternative reading frame). Both are acting as tumour suppressors. The tumour-constraining CDKN2A network regulates two critical cell cycle regulatory pathways, the Retinoblastoma (Rb/RB) pathway and the TP53/p53 pathway. Wild type CDKN2A prevents cancer formation by mediating asenescence-like state upon oncogenic stress. CDKN2A acting as a brake on the cell cycle (p16) and by stabilizing p53 respectively. If CDKN2A 34 function is lost the opposite will occur with uninhibited cellular division, growth and proliferation .

The growth-promoting Ras signalling network with two cascades;

(RAS/MAPK and RAS/PI3K/AKT).

The NRAS proto-oncogene encodes the N-Ras/NRAS protein and is frequently (20%) found in its mutated oncogenic form in melanoma. Mutated forms of the RAS protein are constantly active, and in this state they activate e.g. the plasma membrane bound protein B-Raf / BRAF (akinase) and the PI3K (phossphatidylinositol-3-kinase). The RAS signalling network regulates cell growth, survival and invasion through two cascades.

(i) the RAS/BRAF/MAPK (mitogen-activated protein kinase) pathway, a major stimulus of melanocytic proliferation.

(ii) (ii) the RAS/PI3K/AKT signalling stream, a promoter of melanoma progression and antiapoptosis/survival.

The RAS network with two cascades and the important steps with p16, p14ARF, Rb and TP53, regulating proliferation, DNA repair and apoptosis as well as growth and pro survival signalling. RTK= receptor tyrosine kinase, RB= Rb= Retinoblastoma protein, which in a native (hypo phosphorylated state) binds and inhibits the E2F transcription factor. This type of inhibition preventing G1-to-Stransition of the cell cycle, phosphorylation of RB, thereby inhibiting RB. E2F=a transcription factor. P16 inhibits the Cyclin D1/CDK4-mediated phosphorylation of RB. P14ARF inhibits human homolog of double minute 2 (HDM2), which otherwise inhibits the action of/accelerates the degradation of p53/TP5. Isolated activation of the MAPK pathway leads to secretion of Insulin-like growth factor binding protein 7 (IGFBP7), which in turn induces senescence through suppression of MAPK, as seen in common nevi. Melanomas however, block the IGFBP7 expression (in a so far unknown way) and escape this negative feed back loop, which leads to uncontrolled proliferation .

The PI3K/AKT pathway is important in regulation of apoptosis, cell cycle progression, cell growth (cell mass increase), cell proliferation and survival gene transcription. Many Alterations in the PI3K pathway have been reported in 50-60% of melanomas. A further key component of the PI3K pathway is phosphatase and tensin homolog, another tumour suppressor gene, which is commonly altered (12-50%) in melanoma . Wild type PTEN acts as a tumour suppressor by removing phosphate groups and ctivates / dephosphorylates PI3K, and thereby suppresses cell survival and cell proliferation. Loss of PTEN is often found in combination with BRAF mutations in melanomas on sites without chronic sun-exposure. PTEN has further been shown to be mutated in gliomas and endometrial cancers. germline mutations of PTEN have been found in cancer susceptibility syndromes (e.g. Cowden syndrome) .

The effector of the PI3K pathway is Akt/AKT=protein kinase B/PKB, and the subsequent proliferation, survival and invasion are promoted through AKT. AKT is inhibiting apoptotic processes, thereby promoting cell survival (see below).

• The regulator of melanoma cell apoptosis; the BCL-2 and p53 network. Two apoptotic pathways exist and converge: the intrinsic and

the extrinsic. Both pathways mediate cell death and they are important in understanding the survival as well as the chemotherapeutic resistance of melanomas. The intrinsic (mitochondrial) pathway is activated through several factors (including hypoxia, loss of growth factors and DNA damage) and is regulated bythe big B-cell lymphoma (BCL) - family of proteins. BAK are finally responsible for mitochondrial permeabilization, which in turn leads to activation of caspases and apoptosis. The MAPK and PI3K/AKT pathways (see above) interact with the intrinsic pathway (Wang et al. 2007) and p53 up regulates the transcription of several pro-apoptotic genes e.g. BAX, PUMA and NOXA .

The extrinsic pathway involves activation of “death receptors” in the plasma membrane and downstream activation of caspases. This activation of caspases finally leads to apoptosis, as well as an activation of BID that interferes with the intrinsic pathway. 37 The balance between apoptosis and survival is delicate, both in normal MCs, nevi and melanomas, and high levels of anti apoptotic proteins have been found both in MCs, common nevi and in melanoma, which could partly explain the resistance to apoptosis .

The tumour stem cell theory

A new model of cancer development has been suggested involving research about tumour /cancer stem cells (TSC/CSC). The model suggests that tumours, like melanoma, contain a subset of cells that is capable of both self-renewal and of giving rise to differentiated progeny If the growth potential of melanomas is based on a rare subset of melanoma stem cells, it is important to find out how to eradicate these cells. The TSC theory might explain how thin melanomas can metastasize and why metastatic melanomas are so difficult to treat. Nevertheless, the cell of origin to the TSC is still not known.

PATHOLOGY

The major histo pathological types of malignant melanoma are as follows. Following histo pathological types has been traditionally described but prognosis is not dependent on the following descriptions but rather upon TNM staging.

1. Superficial spreading melanoma
2. Lentigo malignant melanoma
3. Acral lentiginous melanoma
4. Amelanotic melanoma
5. Nodular melanoma

SUPERFICIAL SPREADING MELANOMA

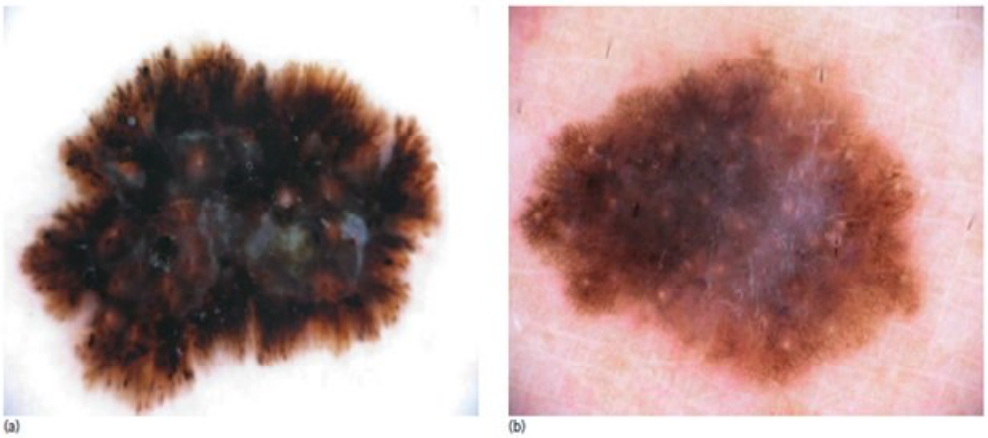
Majority of patients included in this type upto 70%. Superfiial spreading mostly arise from pre existing nevus.

LENTIGO MALIGNA MELANOMA

This type constitute a small percentagae of malignant melanoma (4 to 10%) Lentigo maligna type are generally large size usually more than 3 cm at diagnosis before turn to invasive melanoma. More of patient in this type presented with long duration of in situ lesion. In general lentigo maligna type occur in more than 50years. Older white female are more commonly affected by this type.

AMELANOTIC MELANOMA

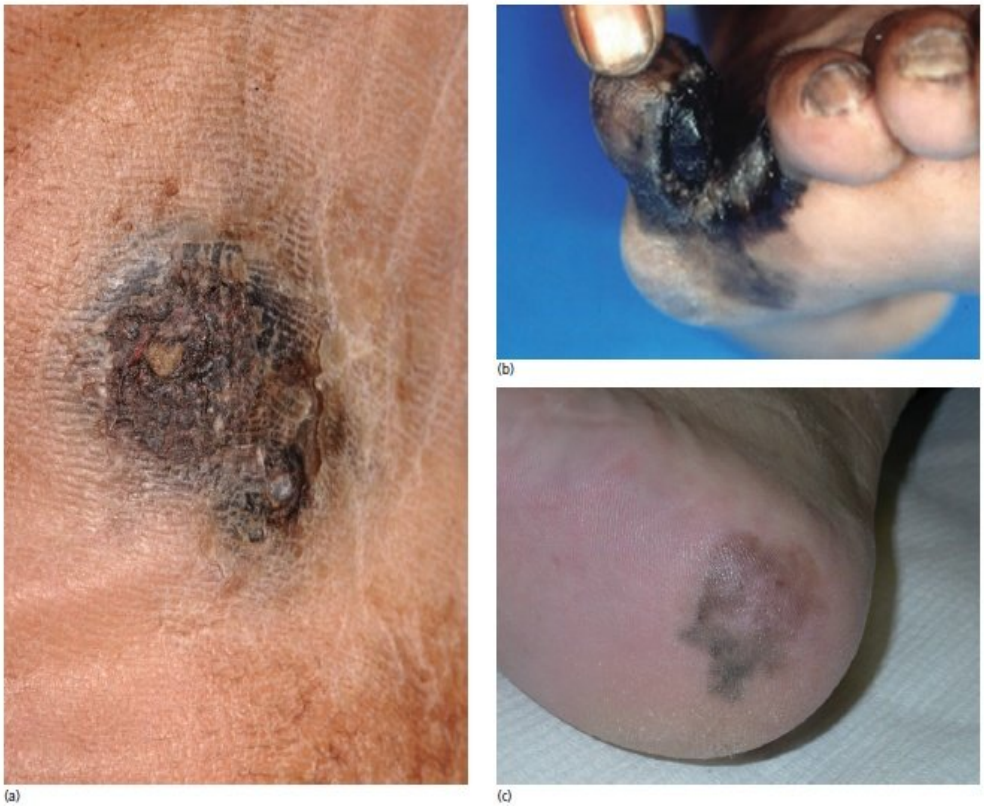
Darkish pigmentation changes not occurred in this types. More unlikely present and diagnosis is very difficult because of their lack of pigmentation. Factors such as change in size, asymmetry and borders irregular suggest possibility of amelanotic type of melanoma



Dermoscopic appearance of superficial spreading melanoma

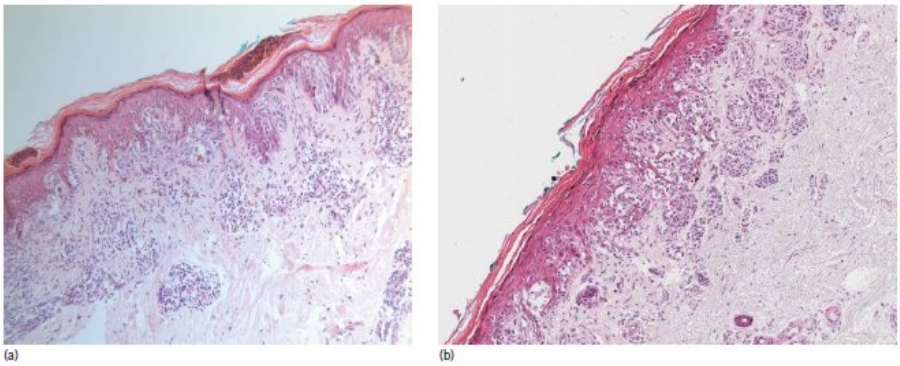
Two nodular melanoma patients

Oral cavity mucosal melanoma



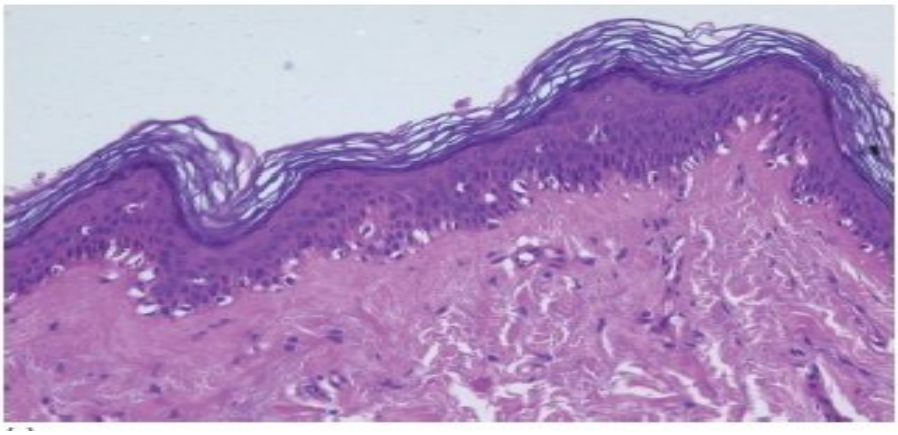
Acral lentiginous melanoma arising from the sole of the foot

Subunguval melanoma

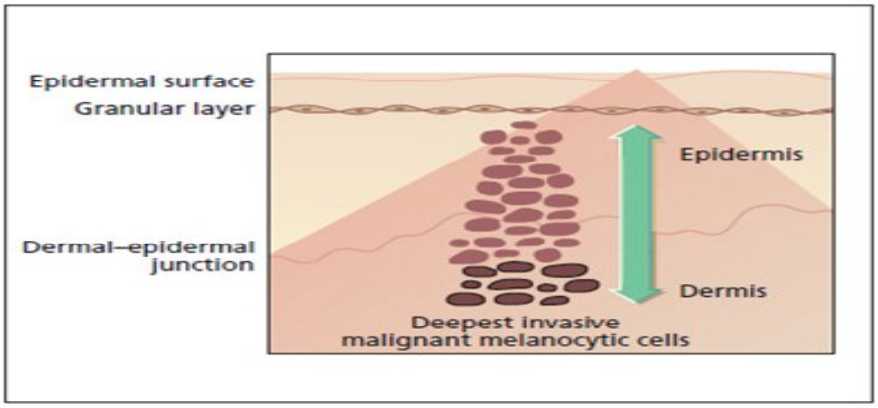


a) Histologic appearance of in situ melanoma with atypical melanocyte within epidermis

b) Superficial spreading melanoma Types-more proliferation of tumor cells in the epidermis



Lentigo melanoma types-very early lentiginous proliferation



CLARK'S LEVEL FOR DEPTH OF INVASION

1-Lesion confined to the epidermis**,**

2 - Lesion extending to the papillary dermis

3- Lesion filling the papillary dermis,

4 -Lesion invading the reticular dermis

5- Cells invading the subcutaneous fat

BRESLOW TUMOR THICKNESS

The pathologist measures in millimetres the distance between the granular layer in the epidermis and the deepest invasive melanoma cell

1) <1.0mm
2) 1.01 to 2.0mm
3) 2.01 to 4.0mm
4) >4mm

DIAGNOSIS

Biopsy of primary lesion is mandatory for histo pathlogical confirmation. Choice of biopsy varies depends upon site of lesion as well as shape of lesion. Excisional biopsy or an incisional biopsy using a scalpel or blade is acceptable. Punch biopsy performed if patients presented with proliferative growth. Full thickness biopsy into the subcutaneous tissue mandatory for proper T staging. Small sizemelanoma should be excised with 1 to 3 cm margin.

Fine needle aspiration cytology used for diagnosing of nodal and extra nodal systemic metastases. FNAC not used for diagnose primary melanoma. Ultrasonagram and magnetic radiological imaging of primary melanoma helpful for extent, adjacent structure involvement. USG more commonly used for diagnose nodal region if clinically not identified. CT chest, abdomen and CT brain more useful for diagnose of any systemic spread.

TREATMENT

MANAGEMENT OF LOCAL DISEASE

Surgery is primary modalities of treatment of early stage of malignant melanoma. Wide local excision is generally done in early stage of melanoma. Wide local excision means wide excision of tumor down to but not generally including the deep fascia with margin of normal skin.

TUMOR THICKNESS	EXCISION MARGIN
In situ lesion	0.5 to 1 cm
<1mm	1cm
1-2 mm	1-2 cm
2-4 mm	2cm
>4 mm	2cm

Usually thin melanoma size of < 1mm adequate margin 1 cm is needed for wide local excision. Intermediate melanoma size of 1-2 mm, wide local excision with 1-2 cm margin. Intermediate melanoma size of 2-4 mm excised with 2 cm margin. Thick melanoma >4mm size excised with 2 cm margin.

WOUND CLOSURE

Various options available for wound closure include primarily closure, local advancement flap, graft and distant flaps. Primarily closure is the treatment of choice for most of early melanoma. Longitudinal incision used for extremities melanoma. skin crease incision require for trunk and head and neck melanoma. Wide local excision included removal of growth, skin and subcutaneous tissue are removed down to deeply but deep fascia not included in excision specimen.

Lazy ‘s’ pattern of incision oriented to allow primary closure. Two layer of closure is usually performed in wide local excision. A dermal layer using 3-0 absorbable sutures. More importantly orientation of specimen is must for accurate assessment of histopathological margins.For extremities melanoma, generally skin graft must be harvested from opposite limb. Usually graft harvested away from the satellite lesion and in transit lesion. Satellites lesion usually occur within 2 cm of primary lesion. Intransit lesion usually present 2 cm beyond the primary lesion but within regional nodal basin. Local advancement flaps is mostly tried if primary closure is not possible. Transposition flaps, distant flaps and rotation flaps of many varieties

used for wound closure if primary closure and local flap not possible for closure of lesion after wide local excision.

Mucosal melanoma including mucosa of respiratory tract, anal canal and vagina had generally poor prognosis. For these mucosal melanoma, generally not advice aggressive surgical treatment. Abdomino perineal resection not generally recommend for anal canal melanoma. Local excision of anal canal is mostly done for all patients. Adjuvant radiation therapy given for mucosal melanoma to reduce the risk of loco regional recurrence.

MANAGEMENT OF REGIONAL LYMPH NODES

Two terminology commonly used in treatment of regional lymphnodes. Clinically and imaging studywise palpable lymphnode or nodal secondaries confirmed by fine needle aspiration cytology, these positive nodal secondaries patient treated with delayed or therapeutic lymph node dissection (TLND). Clinically node negative lymph node patients treated with prophylactic or elective lymph node dissection (ELND).More recently selective approach to regional lymph node followed by most of surgeon especially in treatment of melanoma. Sentinel lymph (SLN) identification developed by mortan et al. Another

recent technique is intraoperative lymphatic mapping used for diagnosis of clinically negative, FNAC negative, N0 node patient.

THERAPEUTIC LYMPH NODE DISSECTION

Patients with known regional lymph node metstases undergo therapeutic lymph node dissection. Main drawback of TLND is delaying treatmet until appearance of lymph node metastases are both clinically and imaging studywise detectable positive lymph node secondaries. These delaying of treatment may result in development of distant micrometastases at the time of lymphadenectomy. Reduced curative rate for above patients.

ELECTIVE LYMPH NODE DISSECTION

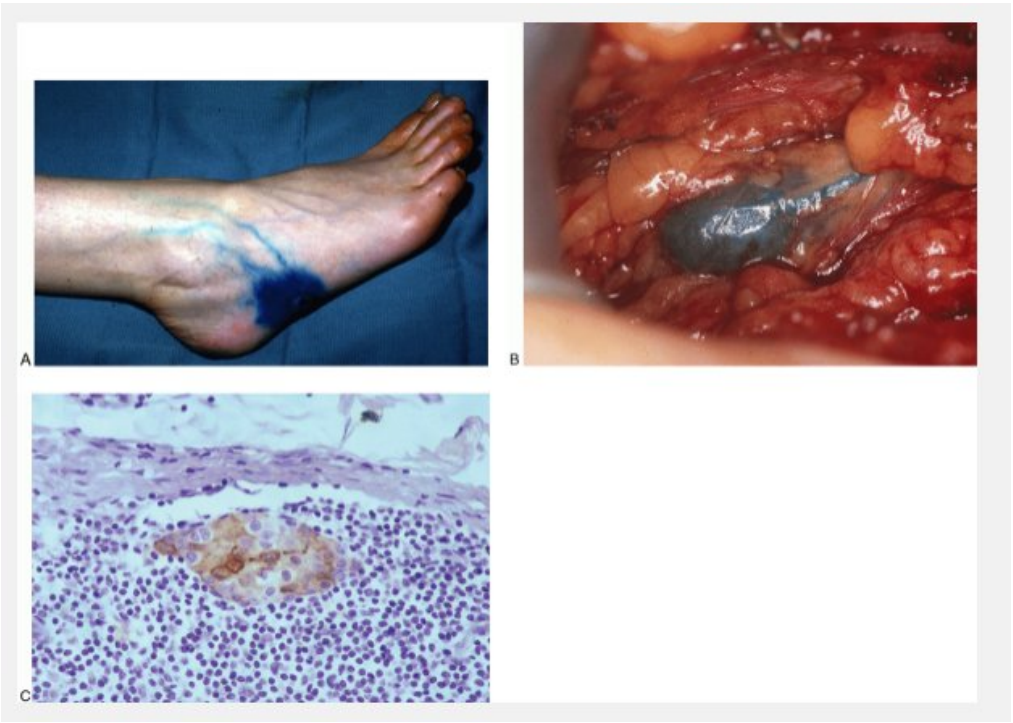
In early stage of melanoma, theoretical advantage of treating lymphnode metastases in the natural history of the disease. Main drawback of ELND is that many patients undergo lymph node surgery who do not have regional lymph node metastases. Better chance of prognosis (50 to 60%) in patients with clinicall negative, FNAC wise positive lymph nodes undergo elective lymphnode dissection compared to patient did not undergo elective lymphnode dissection. Thin type of melanoma size of less than 1 mm not benefited by sentinel lymphnode

dissection because lymph node involvement very rare in thin melanoma. Mostly intermediate type of melanoma size of 1 to 4mm patient mostly useful for intraoperative lymphatic mapping and sentinel lymphnode biopsy.

SENTINEL LYMPH NODE BIOPSY TECHNIQUE

Lymphatic mapping and SLND is performed mostly in N0 patients (clinically and radiologically negative lymphnode). Isosulfan blue dye used for staining the primary node. blue dye injected around the tumor site or biopsy site and the isosulfan blue dye is taken up by the lymphatic system and spread thorough afferent lymphatic to the primary node in regional drainage area. (sentinel node) sentinel node is first draining lymphnode are identified by uptake of isosulfan blue dye . 85% cases of sentinel node approximately identified by use of isosulfan blue dye alone. Remaining 15% of cases not benefited by sentinel lymphnode biopsy. Overcome the false negative result of sentinel lymph node dissection. More recent advanced techniques have been used for significantly improved SLN localization a) pre operative lymph scintigraphy b) Intraoperative technetium 99 labeled sulphur colloid scan c) Intraoperative use of hand held gamma probe.

Technique of intra operative lymphatic mapping and SLNB



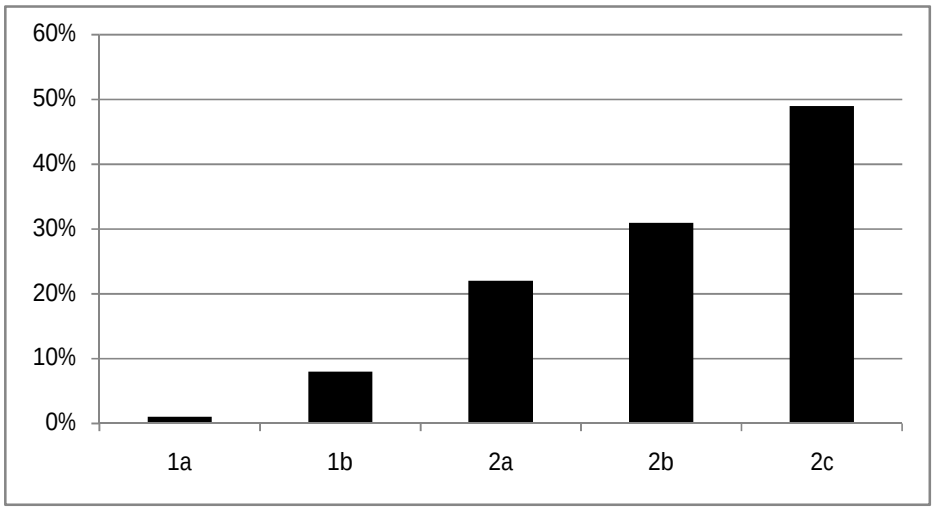
Radioisotope labelled tracer is generally injected intra dermally 3hours preoperatively

A-at the time of surgery

B-sentinel node identified preoperatively

C-pathologic examination by serial sectioning demonstrates a sub scapular nodal metastasis

INCIDENCE OF POSITIVE SENTINEL LYMPH NODES



Stage 1a- 1%

stage 1b – 8%

stage 2a – 22%

stage 2b – 31%

stage 2c – 49%

The incidence of positive sentinel lymph nodes for stage 1a, 1b, 2a, 2b , and 2c were 1%, 8%, 22%, 31% and 49% respectively.

PATHOLOGIAL EVALUATION OF SENTINEL LYMPH NODES

Usually fever lymph node submitted to pathologist by sentinel lymph node technique compared with complete lymph adenectomy. Several antibodies directed against melanoma associated antigens like s-100, HMB-45, tyrosinase, MART-1 and MAGE3 are commonly used for immune histochemistry study. S-100 is low specificity and more sensitive antibodies. HMB-45, MAGE 3 and tyrosinase is more specificity and low sensitivity. Frozen section evaluation is controversial for sentinel lymph node evaluation in management of malignant melanoma. Formalin fixed, paraffin embedded samples block generally used for examination of sentinel lymphnode examination. other technique is touch preparation or cytologic analysis of specimens are used. Sometimes even combination of IHC and histological examination of sentinel lymph nodes may fail to diagnose isolated melanoma cells or oligocellular deposits. With use of reverse *trascriptase – polymerase chain reaction (RT_PCR)identify even in background* 1 * 1000000 to 1* 10000000 normal cells can be identified.

Current practise guidelines for the case of sentinel lymphnode biopsy.

Thin melanoma (<1 mm) not indicated for sentinel lymph node biopsy because overall very very low incidence of positive lymphnode identified by SLNB technique. Identification of doing SLNB is patients who are stage 1b (<1 mm thick with ulceration or mitotic rate >1 mitosis per mm square or 1 to 2 mm thick without ulceration).Stage 2a and stage 2b (1 to 2 mm thick with ulceration or >2mm thick) patients have indication for performing sentinel lymph node dissection. NCCN does not recommend in low risk patients like breslow thickness <0.5 mm and< mitosis per mm2 for performing sentinel lymohh node biopsy.

AXILLARY DISSECTION

Complete axillary dissection means all three level node in axilla must be removed. Axillary node include anterior, posterior, central, lateral and apical lymp node. Horizontal, ‘s’ shaped incision used generally. Skin flaps are raised in all four direction. Important vital structure include nerve to lattismus dorsi, nerve of bell, axillary vessel and cephalic vein preserved. All node level 1, 2 and 3 removed. Hemostasis secured. 15 F closed suction catheter is kept in axilla cavity

through the inferior flap. Drainage tube removed postoperatively secretion if less than 30ml per day for two consecutive days or minimum3-4 wks duration after surgery.

GROIN DISSECTION

A reverse lazy s incision is mostly used for groin lymph node dissection. Incision start from superomedial to the anterior superior iliac spine. Incision extend vertically down to inguinal crease, obliquely across the inguinal crease. Skin flap raised medially upto pubic tubercle, laterally to the lateral border of sartorius muscle. Skin flap raised vertically 3 to 5 cm above the inguinal ligament and vertically below upto apex of the femoral triangle. All the node in inguinal region both vertical and horizontal group removed along with lymphatics. Cloquet's node is important node for whether iliac dissection need or not. Femoral nerve and femoral vessel must always preserved. Only great saphenus vein removed if wanted. Sartorius musle transposition used to prevent the exposed femoral vessel. DT kept in all cases. Drainage tube removed if less than 30 ml per day for two consecutive days. Mostly 3 to 4 weeks, the drainagae tube are removed.

INDICATION OF THE ILIAC AND OBTURATOR NODES

a)Involvement of iliac and obturator node diagnosed pre operatively

b) Superficial lymph node dissection specimen show more than three grossly positive lymph node.

c)Frozen section examination show positive of cloquet's node metastasis.

ADJUVANT THERAPY FOR LOCOREGIONAL DISEASE

A. INTERFERON ALPHA 2b
B. CHEMOTHERAPY
C. RADIOTHERAPY
D. MONOCLONAL ANTIBODIES

INTERFERON ALPHA 2b

High dose interferon alpha 2b is used for patients with melanoma who have a high risk of recurrence. Patients with locally advanced disease, recurrent disease, nodal recurrence, in transit or satellite disease are indication for high dose interferon alpha 2b. Doses of interferon alpha 2 b was 20 million unit/m square/day itravenously for 4 weeks followed by 10 million units per m square three times a week

subcutaneously for nexy 2 days. Recently PEG-IFN ALPHA-2b approved for treating gross nodal and microscopic secondaries melanoma patients. This drug treatment should be started within 3 month of definitive surgical procedure. Doses recommendation is 6microgram/kg/week subcutaneously for 8 doses followed by 3 microgram/kg/week subcutaneously for upto 5 years.

CHEMOTHERAPY

Most of the study describe no benefit of use of adjuvant chemotherapy in melanoma patient who are at high risk for relapse. Only some benefit of survival who treated with adjuvant chemotherapy.

MONOCLONAL ANTIBODIES

Iphilimumab is monoclonal antibodies now being studied in adjuvant treatment setting.

MANAGEMENT OF IN TRANSIT DISEASE

Recurrent local regional disease found in the dermis or subcutaneous tissue beyond 2 cm away from primary lesion but within primary nodal drainage region. 3 to 9% of cases presented with in transit lesion. Chance of occurrence of in transit lesion is high who presented with lower extremity primary tumor, age more than 48 yrs

,thick melanoma according to breslow thickness, ulceration and nodal involvement.

In patient with in transit lesion, more than 60% chance of regional lymph node involvement. More chance of disease recurrence in patient had positive sentinel lymph node, size of in transit tumor more than 2 cm, disease free interval less than 12 months before occurrence of in transit recurrence.

Melanoma patients with in transit metastases confined to limb not amenable for standard surgery, regional chemotherapy techniques is used. Two type of regional chemotherapy used such as isolated limb perfusion and more recently isolated limb infusion. Amputation is rarely indicated nowdays.

HYPERTHERMIC ISOLATED LIMB PERFUSION

Melphalan is used in isolated limb perfusion traditionally. Procedure, first cannulae are inserted and tourniquet is applied at upper level of limb followed extremity is placed on extra corporeal by pass circuit. 8% to 82% response (complete response rate-41%, partial response rate- 31%) can be achieved with use of regional chemotherapy technique with melphalan alone. High complete response rate 88% are

achieved with combination chemotherapy. More commonly following combination chemotherapy are used include melphalan, tumor necrosis fator alpha, interferon gamma. These type of regional chemotherapy technique take long operating times, expensive equipment procedure is complex and invasive and considerable ancillary staff. In an attempt to achieve similar result, a new regional chemotherapy technique, isolated limb infusion has been recently developed.

ISOLATED LIMB INFUSION

Low flow perfusion performed via percutaneously inserted catheters. Oxygen circuit not used in isolated limb infusion. Here catheter inserted into unaffected limb and catheter advanced intravascularly to the tumor limb. General anaesthesia needed for performing this technique. Generally melphalan and actinomycin-D types of chemotherapy used. Main mechanism of these technique damage of tumor cells are more effectively occurred under hypoxia and acidosis. Overall response rate 82% (complete response rate 38%, partial response rate 40%)

MANAGEMENT OF LOCAL RECURRENCE

Single lesion of local recurrence in patient with primary melanoma had good prognosis treated with wide local excision similar to primary treatment. Multiple, small and superficial lesion may be treated in a similar way to that used for patients with in transit disease.

MANAGEMENT OF DISTANT METASTASES

Common sites of recurrence in decreasing frequency order, distant skin and subcutaneous tissues (39%), lungs (11 to 34%), liver and brain. Poor prognosis in patient with systemic metastasis had lower survival ranging from 6 to12 months. Only palliative use of radiotherapy and chemotherapy if patients with systemic metastasis but little benefit of palliative treatment. surgery is also a very useful palliative treatment for isolated accessible distant metastases.

TARGETED THERAPY

a)BRAF inhibitors

The BRAF gene encodes for origin of B-RAF , a protein involved in tumor growth. BRAF mutation have been identified in 50% of invasive cutaneous melanoma. BRAC inhibitors, PLX4032

(vemurafenib) used in unresectable, stage 3 c or stage 4 melanoma patients with presence of mutated BRAF gene.

b) KIT Inhibitors

Single agent chemotherapy generally used for metastatic melanoma. Dacarbazine is the drug of choice used for distant metastatic melanoma. Dartmouth regimen (dacarbazine, cisplatin, carmustine and tamoxifen) also used, response rate 55% overall and complete response rate 20% in patient treated with Dartmouth regimen.

RADIATION THERAPY

A case were inability to obtain wide margins, satellitosis, desmoplastic melanoma, adjuvant radiation to primary tumor region more useful. Adjuvant radiation to regional nodal region has been clearly defined. Indication of adjuvant radiotherapy include multiple positive nodes, one or more metastatic node more than 3 cm and extranodal spread.

External beam radiation therapy provide long term local control and more effective palliation. Recurrent subcutaneous and nodal disease, symptomatic bone metastasis benefited by adjuvant radiation therapy.

FOLLOW UP AND SURVEILLANCE

Early Stage melanoma (insitu or <1 mm thick, non ulcerated, no lymphnode)	Every 6 months for 2 years and then annually
Thicker or ulcerated melanoma or positive lymphnode	Every 3to 4 months upto 3 years, every 6 months next 2 years and then annually

At each visit, patient undergoes a physical examination, skin survey and serum LDH level. Radiographic evaluation is generally not performed in stage 1 and stage 2 melanoma. Chest x ray is generally done at each follow up except in situ and thin melanoma. Stage 3 (or) stage 4 disease CT or PET/CT scan should be considered every 6 to12 months. Patients with stage 3c or stage 4 melanoma, MRI of the brain can be considered. USG of regional lymph node not well established for surveillance of patients with stage 1 to 3 disease.

MATERIALS AND METHODS

SELECTION OF CASES

Cases admitted in all surgical units of department of general surgery, dermatology department, plastic surgery department and oncology department in Stanley government hospital between may 2011 to December 2013 were taken in a random fashion for this study. This group of 30 patients were aged between 30 to72 years with a mean age of 50 yrs. Of these 18 were male and 12 female.

Patients with blackish discoloration of skin were admitted with a provisional diagnosis of malignant melanoma. 10 cases were admitted in this fashion. 2 cases present with oral blackish discoloration.

Seven patients presented with growth in skin, 2 patients presented with ulcer in skin, 4 patients presented with swelling in lymphnode region and 5 patients presented with anal growth.

INVESTIGATIONS DONE

All the patients admitted in surgery department underwent baseline investigations including complete hemogram, urine analysis,blood sugar, renal function tests like blood urea and serum creatinine, and serum electrolytes. All patients had liver functions tests done and one patients with liver secondaries had elevated bilirubin - 4mg% with a normal SGOT,and SGPT serum albumin was low in in patient 2.8g%.

Three patients were known diabetic on oral hypoglycemic drugs and two patients was found to be a diabetic. Chest x ray and ECG was done in all patients. No patient in our series had brain . All patient underwent full thickness biopsy of growth and blackish discoloration lesion was sent for histopathological examination and confirmed as malignant melanoma of various region like cutaneous and mucosal melanomas. Serum LDH, USG abdomen was done in all patients.

MRI of primary region done only for clinically locally advanced disease patient. USG of primary nodal basin region done for clinically non palpable locally advanced and metastatic disease patients .CT brain, CT chest and CT abdomen done only for suspicious metastasis patients.

One patients presented with lung secondaries. None of the patients underwent sentinel lymph node biopsy.

All patients after admission were hydrated well with IV fluids and compatible blood transfusion were given in 2 patients with anaemiaand their general condition and nutritional status were improved. Diabetics patients, glycemic status controlled with insulin and cancer treatment was then planned.

RESULTS

These 30 patients were divided into two main group. Group A were curative resection was planned and Group B were palliative treatment was planned.

GROUP A

Included 24 patients for curative resection

- no distant visceral metastasis
- no local fixity to surrounding important structures
- no fixed regional lymphnode

GROUP B

Included 6 patients for palliative treatment

- Palliative resection (2 patients)
- Palliative chemotherapy (2 patients)
- Palliative radiotherapy (3 patients)

SURGERY IN GROUP A PATIENTS

24 patients of this group underwent a wide local excision by skin crease incision in trunk, longitudinal incision in extremities 7 patients of this group underwent therapeutic radical lymphnode dissection with wide local excision. No local fixity to bone and neurovascular bundles, no fixed metastatic lymphnode, no distant visceral metastasis like liver, lung and brain in group A patients.

TREATMENT IN GROUP B PATIENTS

6 patients belonging to this group. Two patients presented with distant visiceral metastasis, one presented with extremities growth with liver secondaries. Another one patient presented extremities growth, inguinal lymphnode bilateral fixed node with involvement of lung secondaries. These above two patients underwent palliative radiotherapy and palliative chemotherapy. Three patients presented with unresectable extremities growth with fixed lymphnode metastasis. These three patient underwent palliative chemotherapy and palliative radiotherapy. One patient presented with in transit lesion and this patient underwent palliative chemotherapy and isolated limb perfusion.

POST OPERATIVE PERIOD

All the patients underwent wide local excision with therapeutic radical lymphnode dissection hada continuous drainage tube for a period ranging from 2 weeks to 3 weeks. 5 patients underwent abdominoperineal resection. These 5 patients had a continuous intraabdominal drains were removed on day 10 to 14th day and most of the patients were discharged on day 8 on the average and were reviewed regularly for follow up.

5 patients developed wound infection and gaping and had to undergo secondary closure. 3 patients developed flap necrosis and had to undergo flap revesion and skin graft. Two paients keep the draiage tube in nadal region for 4 weeks and managed conservatively.

FOLLOW UP

All the patients advised regular follow up every 3 to 4 months for first 2 years palliative chemotherapy was given in 5 patients with decarbazine, cisplatin and vinblastine chemotherapy. Palliative radiotherapy was given in 2 patients they had good symptomatic relief for few months, but few patients lost follow up after 6 months.

Among group B patients, 4 patients develop distant metastasis. Among group A patients, 5 patients develop local recurrence, these 5 patients underwent wide local excision with radiotherapy. 1 patient develop recurrence distant skin and subcutaneous tissue and this patients underwent debulking excision, palliative radiotherapy and chemotherapy.

DISCUSSION

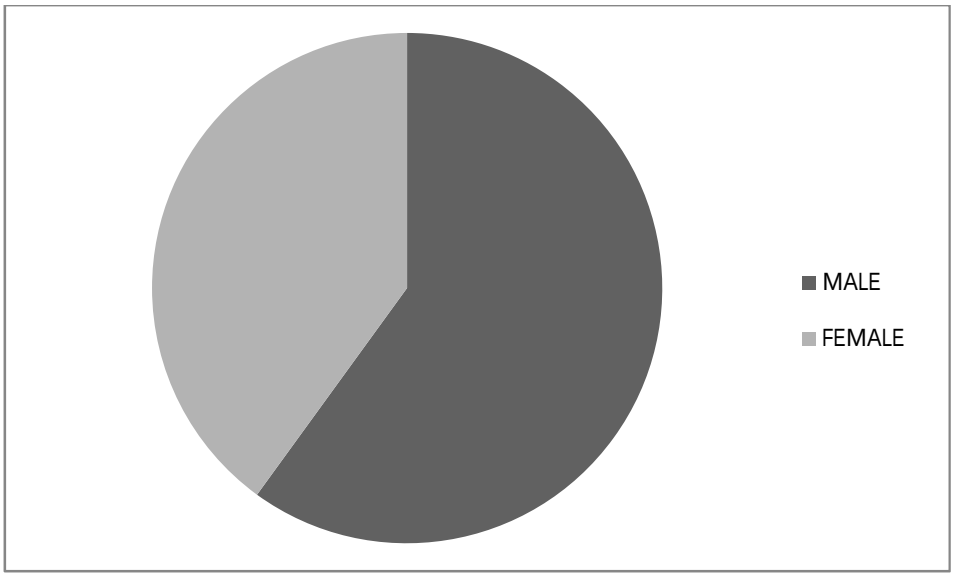
In our series of 30 patients, proved to have malignant melanoma, male comprised 60% and females only 46%.

SEX	NO	%
Male	18	60%
Female	12	40%

Of these patients, most of them fall into the age group 40 to 60years, the range being 30 to 72 years and the mean age being 52 years.

Class interval age in years	No.	%
30-39	4	13.3
40-49	10	33.3
50-59	11	36.6
60-72	5	16.6

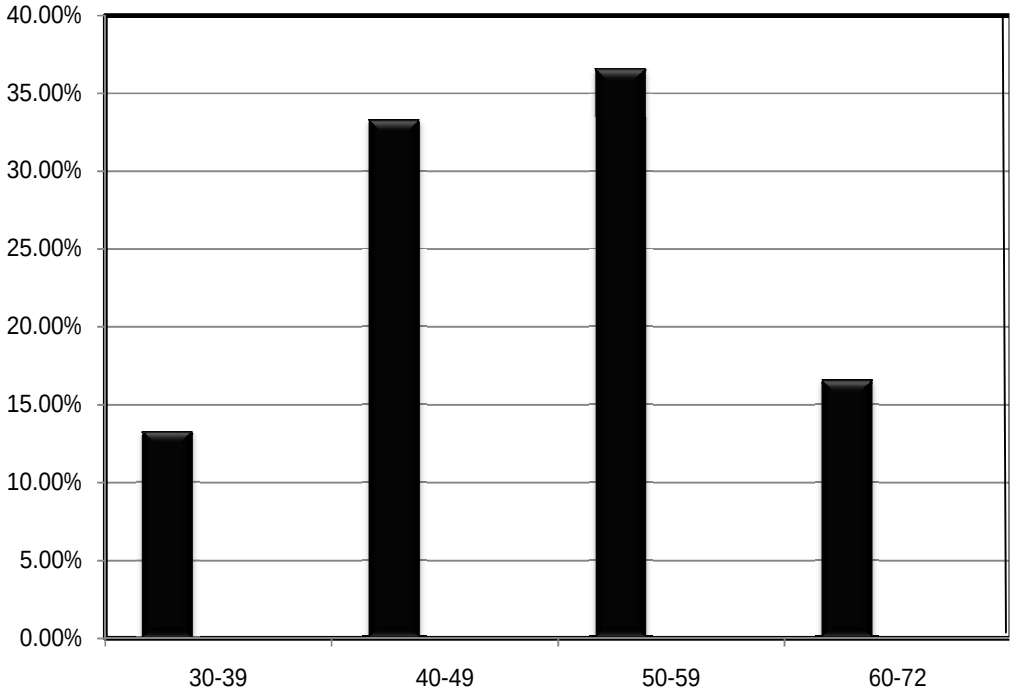
SEX INCIDENCE IN 30 CASES OF MALIGNANT MELANOMA



Male 18 patients (60%)

Female 12 patients (40%)

AGE INCIDENCE IN 30 CASES OF MALIGNANT MELANOMA



30-39years-13.3%

40-49years-33.3%

50-59years-36.6%

60-72years-16.6%

At presentation, 63.3% patients presented with skin growth. 10% patients presented with ulcer lesion. 12% patients presented with blackish discoloration of skin and mucosal site include oral cavity and anal canal region.

SYMPTOM	**NO.**	**%**
Skin growth	19	63.3%
Blackish discoloration	10	33.3%
Ulcer	12	40%
lymphnode swelling	7	23.3%
Anal canal growth	5	16.6%

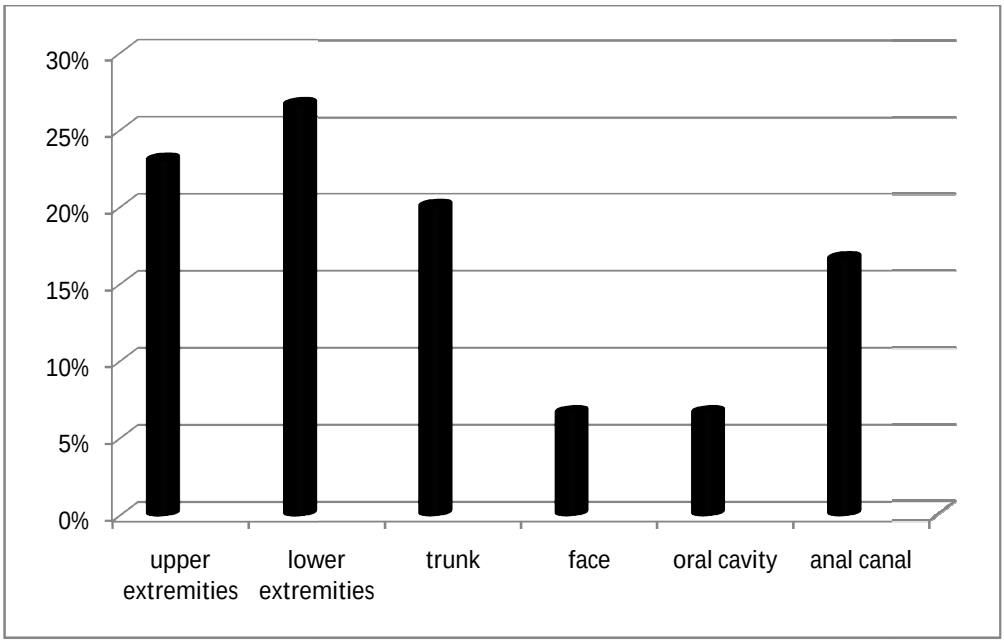
On clinical examination, 19 patients had an growth lesion with or without ulcer lesion. 4 patients had satellite nodule present within 2cm of primary lesion. 1 patient presented with in transit lesion. 4 patients presented with clinically lymphnode metastasis. 2 patients had lymphnode detected by ultrasonogram and CT scan.

SIGN	NO.	%
Growth with or without ulcer	19	63.3%
Satellite nodule	4	13.3
In transit lesion	1	3.3
Lymphnode metastasis	4	13.3
Anemia	2	6.6

At presentation, most of the patients had extremities growth ad ulcer lesion. 15 patients included in extremities melanoma lesion. 6 patients present with growth and ulcer present in trunk. 5 patients had growth present in anal canal. 2 patients had oral cavity and blackish discoloration lesion present.

LOCATION	NO.	%
Trunk	6	20%
Upper extremities	7	23%
Lower extremities	8	26.6%
Oral cavity	2	6.6%
face	2	6.6%
Anal canal	5	16.6%

LOCATION OF MELANOMA INIDENCE IN 30 CASES OF MALIGNANT MELANOMA



1) Upper extremities-23%

2) Lower extremities-26.6%

3) Trunk-20%

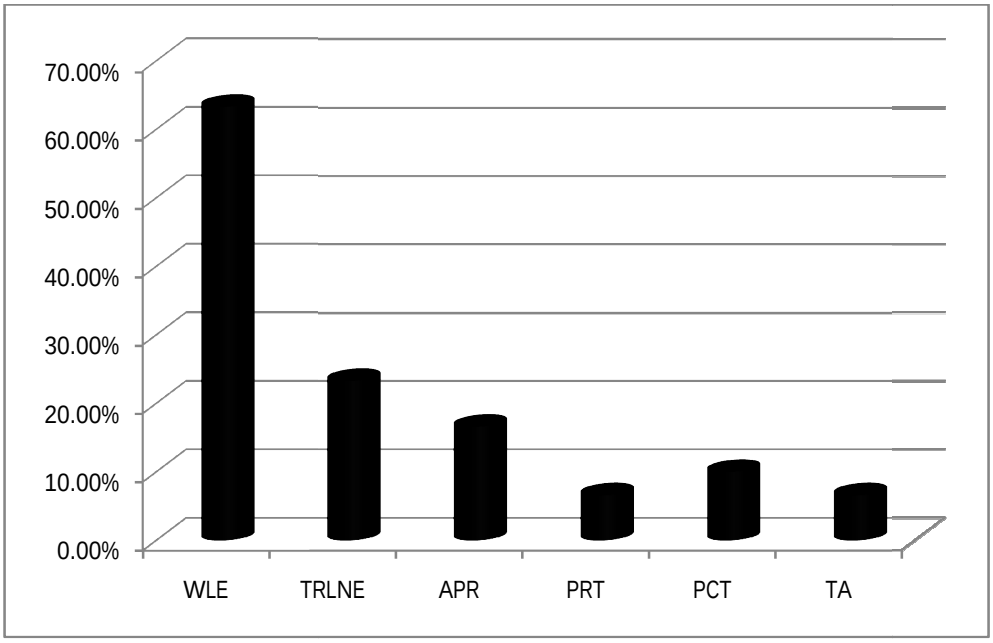
4) Anal canal-16.6%

5) Face and oral cavity each separately-6.6%

Among the 30 patients in our series only 7 patients underwent therapeutic radical lymphnode dissection. Most of the patients could achieve a curative resection. 24 patiets underwent wide local excision. 5 patients underwent abdominoperineal resection. 5 patients completed palliative chemotherapy and radiotherapy.

TREATMENT OPTION	**NO.**	**%**
Wide local excision	19	63.3%
Therapeutic radical Lymphnode dissection	7	23.3%
Abdominoperineal resection	5	16.6%
Toe amputation	2	6.6%
Palliative radiotherapy	2	6.6%
Palliative chemotherapy	3	10%

TREATMENT MODALITIES



1) WLE-63.3%

2) TRLNE-23.3%

3) APR-16.6%

4) PRT-6.6%

5) PCT-10%

6) TA-6.6%

Based on histopathologial examination after resection, the tumour thickness classified based on breslow's description. Thin melanoma < 1mm no patient in my study. Intermediate melanoma thickness range of 1 to 4mm, 36.66% of patients present. Thick melanoma thickness range of >4mm, these class of patients mostly present in my study 73.3% patients included in thick melanoma group.

BRESLOW TUMOUR THICKNESS	**NO.**	**%**
<1.0 MM	_	_
1.01 – 2.0MM	3.3	10%
2.01 _ 4.0MM	8	26.6%
>4MM	22	73.3%

BRESLOW CLASSIFICATION

BLUE-Thick melanoma-73.3%

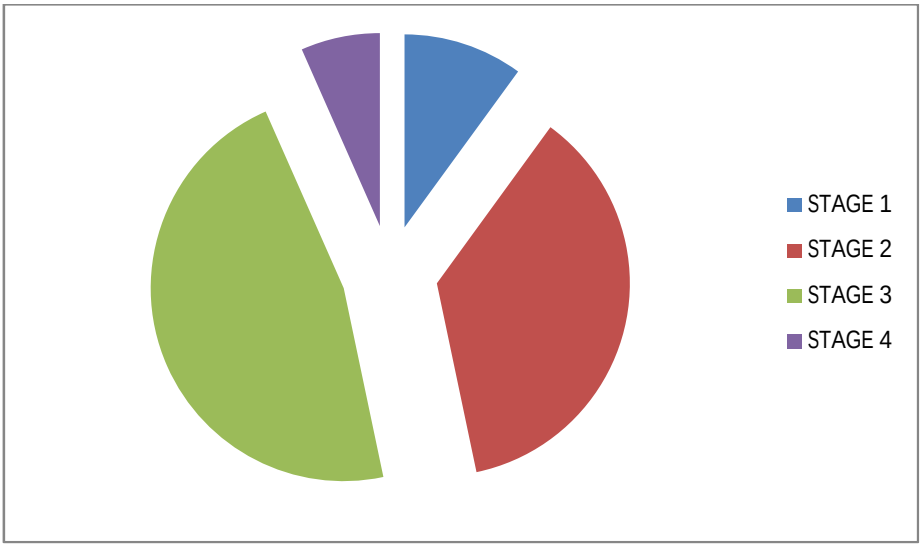
RED-Intermediate melanoma-26.6%

GREEN-Thin melanoma-10%

Based on clinico pathological TNM staging most of the patients in my study included in stage 3. 46.6% patients included in stage 3. 36.6% patients included in stage 3. 36.6% patients included in stage 2. Only few patients presented with stage 1 and 4 diseases.

clinico pathological stages	**no.**	**%**
stage1	3	10%
stage 2	11	36.6%
stage 3	14	46.6%
stage4	2	6.6%

CLINICO PATHOLOGICAL STAGE - TNM STAGING



- Stage 1---10%
- Stage 2---36.6%
- Stage 3---46.6%
- Stage 4---6.6%

In the past operative period, the commonest complication was wound infection and flap necrosis. 8 patients presented with wound infetction. 10% had flap necrosis occurred.Each of the following complicationlike lymphedema, lymphorrhea and paresthesia presented in 6.6% of patients.

COMPLICATION	NO	%
Wound infection	8	26.6%
flap necrosis	3	10%
Lymphorrhea	2	6.6%
Lymphedema	2	6.6%
Paresthesia	2	6.6%

CONCLUSION

- Mean age at presentation was 50 years
- 46.6% of patients had stage 3 disease at presentation
- Most of the cases in this series are extremities melanoma
- Curative wide local excision was possible in 63.3% of cases
- Blackish patches, ulcer and growth were the commonest complaints
- Prognosis of the patients in my study better in patients without ulceration and lymph node involvement.

PROFORMA

- NAME : SL. NO:
- AGE /SEX:
- ADDRESS WITH CONTACT NUMBER:
- IP NO:
- DATE OF ADMISSION:
- DATE OF SURGERY:

HISTORY OF PRESENTING ILLNESS:

- Mole -number, site, color changes, diameter changes, progression
- Growth–size, site, duration
- Ulceration-site, duration
- Swelling in lymph nodal region
- pigmentation of skin

PAST HISTORY:

- WHETHER A KNOWN CASE OF DM/HYPERTENSION/ ASTHMA/TB/EPILEPSY/CARDIAC ILLNESS
- H/O SIMILAR EPISODES IN THE PAST, IF ANY:
- H/O sunlight exposure

FAMILY HISTORY:

TREATMENT HISTORY:

<u>CLINICAL EXAMINATION:</u>

GENERAL EXAMINATION: temp: p.r: bp:

SYSTEMIC EXAMINATION:

CVS

RS

PER ABDOMEN CNS

LOCAL EXAMINATION:

Growth in skin : **present/ absent**

Ulceration: **present/ absent**

Lymphadenopathy : **present/ absent**

Changes in mole: **present/ absent**

CLINICAL DIAGNOSIS:

INVESTIGATIONS:

1.ROUTINE INVESTIGATIONS: CBC, RFT,LFT,CXR,ECG

2.BIOPSY-INCISIONAL/EXCISIONAL

3. USG, CT SCAN, MRI SCAN

4. FNAC OF LYMPH NODE ,SENTINAL NODE BIOPSY

5. SERUM LDH

SURGERY DONE:

HISTO PATHOLOGICAL REPORTS:

FOLLOW UP:

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ANNEXURES

MASTER CHART

S. NO	NAME	AGE	IP NO	SEX	CLINICAL MANIFESTATIONS	TREATMENT	CLINICO PATHOLOGICAL STAGING	RECURRENCE	FOLLOW UP (MONTHS)
1	MANI	46	17684	M	SG, B	WLE	3	L	12
2	KANAN	55	17682	M	SG , B	WLE+TRLND	3	L	8
3	FATHIMABEE	30	17922	F	B	WLE	1	-	18
4	PERIYASAMY	63	38627	M	B	RT , CT	4	LIVER	8
5	RANI	56	38738	F	SG , LN	WLE+TRLND	2	LNR	6
6	MOORTHY	48	38200	M	B	WLE	2	-	15
7	KALAIYARASI	65	17001	F	SG	WLE	3	L	11
8	ISMAIL	50	17212	M	A G	APR	3	L	8
9	CHANDRA	41	27872	F	SG	WLE	2	-	8
10	SUBBARAO	52	27802	M	B	TA	2	-	12

S NO	NAME	AGE	IP NO	SEX	CLINICAL MANIFESTATIONS	TREATMENT	CLINICO PATHOLOGICAL STAGING	RECURRENCE	FOLLOW UP (MONTHS)
11	MALARKODI	32	38500	F	SG , LN, S	WLE+TRLND	2	LNR	14
12	SINGARAM	72	17500	M	SG	WLE	2	-	9
13	RANGANATHAN	48	29100	M	B , U	WLE	2	-	5
14	SAKUNTHALA	68	21000	F	A G	APR+ H +CT	2	SS	11
15	CHANDRU	51	22822	M	SG , B	WLE	1	-	10
16	NAJIH	42	23122	M	SG,LN, S	WLE+TRLND	3	-	7
17	RUKUMANI	43	27100	F	U	TA	3	-	8
18	ILAKIA	69	37100	F	SG , LN	WLE+ TRLND	3	-	10
19	BASKAR	58	36891	M	SG , B	WLE	2	-	18
20	REVATHI	49	36221	F	SG, LN ,S	WLE+TRNLD +RT+CT	3	LNR	7

S NO	NAME	AGE	IP NO	SEX	CLINICAL MANIFESATIONS	TREATMENT	CLINICO PATHOLOGICAL STAGING	RECURRENCE	FOLLOW UP (MONTHS)
21	JOSEPH	56	16722	M	AG	APR	2	-	16
22	VENGATESH	49	16002	M	B, SG	WLE	2	-	12
23	GEETHA	44	18009	F	SG	TA	1	-	8
24	NATARAJ	34	39101	M	B,SG,S	WLE, RT , CT APR	4	LUNG	12
25	KRISHNAVENI	48	24211	F	A ,G	WLE+TRLND	3	-	7
26	MICHAEL	56	24329	M	B,SG, LN, I	+RT + ILP	3	LNR	6
27	RAJA	53	25418	M	SG	WLE	3	-	8
28	RAMANIDEVI	55	17819	F	B , SG	WLE	3	L	12
29	PARTHIBAN	36	17009	M	SG	WLE	3	-	11
30	SRIPRIYA	51	28189	F	AG	APR	2	-	10

ABBREVIATION

A.G –Anal canal growth, S.G –Skin growth, U-ulcer, LN-lymph node swelling , B –blackish patch, S –Satellite nodule, I –Intransit lesion , TA –Toe amputation , APR –Abdominal perineal resection, H–Hystrectomy, WLE –Wide local excision, TRNLD –Threapeutic radical lymph node dissection, RT –Radiotherapy, CT –Chemotherapy, AF –advancement flap, ILP –Isolated limp perfusion, SS –Skin and subcutaneous tissue, L–Local recurrence, LNR –Lymph node recurrence.

REVISED TNM CLASSIFICATION

This classification system was updated in 2009 by the AJCC.

T Classification	***Thickness***	***Ulceration Status***
Tis	N/A	N/A
T1	≤ 1.0mm	a: w/o ulceration and mitosis < 1 / mm^2 b: with ulceration and mitosis ≥ 1 / mm^2
T2	1.01-2.0mm	a: w/o ulceration b: with ulceration
T3	2.01-4.0mm	a: w/o ulceration b: with ulceration
T4	> 4.0mm	a: w/o ulceration b: with ulceration
N Classification	***# of Metastatic Nodes***	***Nodal Metastatic Mass***
N0	No evidence of lymph node metastasis	
N1	1 node	a: micrometastasis b: macrometastasis
N2	2-3 nodes	a: micrometastasis b: macrometastasis c: In transit metastases/satellites without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in-transitmetastases/satellites and metastatic nodes	
M Classification	***Site***	***Serum LDH***
M0	No evidence of metastasis to distant tissues or organs	
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Or any distant metastases	Normal Elevated

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

மெலனோமா புற்றுநோய்

ஆராய்ச்சி நிலையம் : பொது அறுவை சிகிச்சைப்பிரிவு
அரசு ஸ்டான்லி மருத்துவக் கல்லூரி,
சென்னை - 600 001.

பங்கு பெறுபவரின் எண்.

பங்கு பெறுபவரின்
பெயர் மற்றும் விலாசம் :

எனக்கு மெலனோமா புற்றுநோய் இருப்பதை மருத்துவர் மூலம் அறிந்து கொண்டேன். அதற்கு சிகிச்சை செய்தவற்காக எக்ஸ்-ரே, மருந்து செலுத்தி சி.டி.ஸ்கேன், திசு பரிசோதனை, இரத்த பரிசோதனை, நிணநீர் கட்டி திசு பரிசோதனை மூலம் சோதனை செய்ய வேண்டிய அவசியத்தை மருத்துவர் மூலம் அறிந்து கொண்டேன். அதற்கு முழு மனதுடன் சம்மதம் தெரிவிக்கிறேன்.

மேலும் திசுப்பரிசோதனை முடிவுகளும், என்னுடைய மற்ற பரிசோதனை முடிவுகளையும் மருத்துவரும், மருத்துவமனையும் பயன்படுத்திக் கொள்ள முழு மனதுடன் சம்மதிக்கிறேன்.

இது தொடர்பான விளக்கங்களையும் விளைவுகளையும் மருத்துவர் எனக்கு தெரிந்த மொழியில் விளக்கி கூறினார்.

பங்கு பெறுபவரின் கையொப்பம் ..... இடம் ..... தேதி.....

பெற்றோர்/கணவர்/மனைவி கையொப்பம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி.....

தகவல் படிவம்

ஆய்வில் பங்கேற்கும் நோயாளியின் கடமைப் பொறுப்புகள்

உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் நீங்கள் முழுமையாக ஒத்துழைக்க வேண்டும் என்று உங்களைக் கேட்டுக் கொள்கிறோம். சிகிச்சையளிக்கும் மருத்துவர் அளிக்கும் அறிவுரைகளை பின்பற்ற வேண்டும் என்றும், என்னென்ன செய்ய வேண்டும், என்னென்ன செய்யக்கூடாது என்று உங்களிடம் கூறப்பட்டுள்ளவற்றிலிருந்து சற்றும் விலகக்கூடாது என்றும் நீங்கள் எதிர்பார்க்கப்படுகிறீர்கள்.

ஆய்வில் உங்கள் பங்கேற்பு மற்றும் உங்கள் உரிமைகள்

இந்த ஆய்வில் உங்கள் பற்கேற்பு தன்னிச்சையானது மற்றும் காரணங்கள் எதையும் கூறாமலேயே நீங்கள் இந்த ஆய்விலிருந்து எந்த ஒரு நேரத்திலும் விலகிக் கொள்ளலாம். எப்படியிருந்தாலும், உங்கள் உடல் நிலைக்கேற்ப உங்களுக்கு பொறுத்தமான சிகிச்சை அளிக்கப்படும். ஆய்வில் பங்கேற்க நீங்கள் மறுப்பதால், அடுத்து வரும் ஆராய்ச்சி ஆய்வுகளில் உங்கள் பங்கேற்பை மறுப்பது போன்ற எந்த வித அபராதமும் விதிக்கப்படாது. உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் முழுவமையாக ஒத்துழைக்க நீங்கள் சம்மதிக்க வேண்டும். எந்த ஒரு நேரத்திலும், நீங்கள் மோசமாக உணர்ந்தாலோ அல்லது வேறு ஏதேனும் உடல்நலக்குறைவு உண்டானாலோ, தயவுசெய்து, உங்களை கவனித்து வரும் மருத்துவரிடம் உடனடியாக தெரிவிக்கவும். சிகிச்சை உங்களுக்குப் பொருத்தமாக இருக்காது என்று தோன்றினால் உடனடியாக நிறுத்தப்படும். உங்கள் சம்மதம் இன்றியேகூட ஆய்வு நிறுத்தப்படுவது சாத்தியமே. ஆய்வின்பொழுது ஏதேனும் புதிய தகவல் தெரியவந்தால், அதைப்பற்றி உங்கள் மருத்துவர் உங்களுக்கு தெரிவிப்பார்.

ஆய்வில் பங்கேற்பவர்/ சட்டபூர்வமாக
ஏற்கப்பட்ட நபர் கையொப்பம்
அல்லது
பெருவிரல் பதிவு

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Clinico pathological study of malignand melanoma

Principal Investigator : Dr.A.Murugan

Designation : PG in M.S.(Gen.Surgery)

Department : Department of General Surgery
Government Stanley Medical College,
Chennai-10

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.04.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

11/12/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI